Micturition

Introduction

In the last lesson we discussed the segments of the urethra and the histologic changes, mentioning that there is both an external and internal sphincter, but not spending much time on them. Here is where we will spend some time on them. The urethra is just a tube that drains urine out of the bladder. The ureters are just tubes that drain urine into the bladder. There are no sphincters or control-of-flow mechanisms for the ureters. All of this means that the flow of urine is controlled solely at the point of the urethral opening to the bladder. There are three forces at play—detrusor, external sphincter, and internal sphincter. The detrusor muscle surrounds the bladder. When it contracts, urine will flow out of the bladder. The internal sphincter and external sphincter block the exit of urine from the bladder. When they contract, urine flow is restricted. When they dilate, urine flow is permitted. It is the complicated combination of parasympathetic, sympathetic, and somatic inputs to these three structures that is the subject of this lesson.

Micturition Anatomy and Innervation

The bladder is lined by transitional epithelium. It holds the urine. The detrusor muscle surrounds the bladder. Contraction expels urine. From this point forward in this lesson, "bladder" and "detrusor muscle" will be synonymous.

The **detrusor muscle** is smooth muscle. It is innervated by the **parasympathetic fibers** originating at S2–S4, and has **M_3 muscarinic acetylcholine receptors.** Parasympathetic discharge activates M_3 receptors and results in an increase in cytoplasmic calcium. Cytoplasmic calcium in a smooth muscle induces contraction, thereby increasing tension. Increased tension will cause urine to exit the bladder. The detrusor is also innervated by **sympathetic fibers** originating from T10–L12. Sympathetic discharge activates β_2 receptors and inhibits contraction. In addition, the detrusor muscle responds to distention. As urine fills the bladder, bladder distension results in detrusor contraction. If there were no sphincters at all, simply stretching the bladder would cause it to void. This (along with gravity) is what lets an indwelling catheter continuously drain urine.

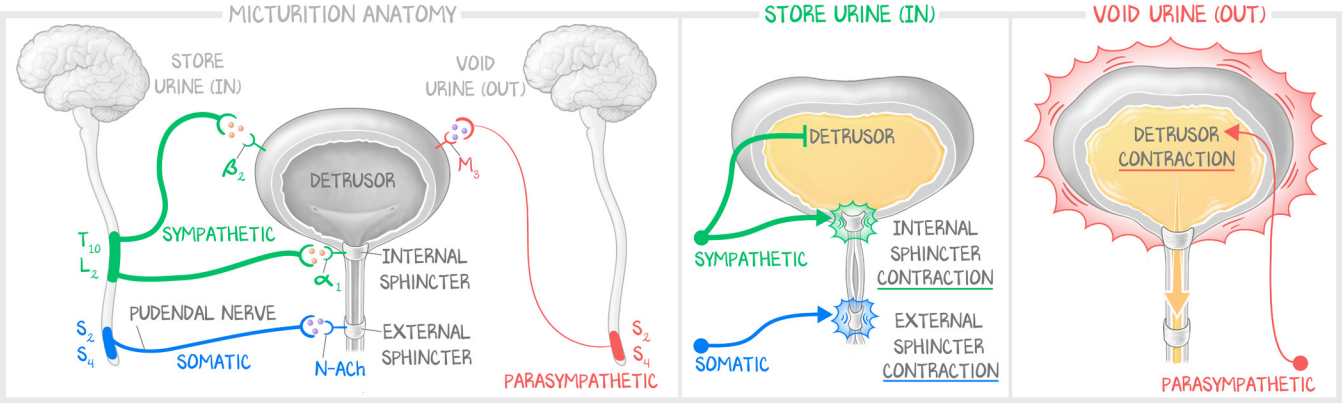

Figure 2.1: Micturition Anatomy
The parasympathetic fibers arise from the sacrum, and innervate the detrusor M_3 receptors. The sympathetic nerve fibers arise from the lumbar spine and innervate both the detrusor and the internal urethral sphincter. The pudendal nerve arises from the sacral plexus and innervates the external sphincter. The internal urethral sphincter is smooth muscle just as the urethra exits the bladder. The external urethral sphincter is skeletal muscle as the urethra passes through the pelvic floor. Contraction of these sphincters holds urine in. The detrusor envelops the bladder, so contraction of the detrusor empties the bladder.

The **internal sphincter** is also **smooth muscle** and is present just after the trigone. The bladder is contiguous with the urethra. The urethra here is still transitional epithelium. Just as the posterior urethra originates from the bladder, the internal urethral sphincter surrounds the urethra. In males, this is above the prostate. It receives **sympathetic signals** from T10–L2, the same fibers that innervate the detrusor. The smooth muscle fibers of the internal sphincter have on them α_1 receptors. Stimulation of α_1 causes contraction.

Sympathetics cause detrusor relaxation and internal sphincter contraction. Sympathetics keep urine in. Parasympathetics cause detrusor contraction. Parasympathetics force urine out, but only when the other sphincters are relaxed.

The **external sphincter** is **skeletal muscle**. It is located distal from the bladder and the internal sphincter. The pelvic floor muscles are also skeletal muscle. The external urethral sphincter is not one of the pelvic floor muscles, but is located very close to them. In males, it is easily identified as being after the prostate. In females, it is effectively immediately proximal to the pelvic floor muscles. The external urethral sphincter is under **somatic control** by the **pudendal nerve**. This is the only muscle in the system that is **voluntary**.

Detrusor Physiology

To understand what the detrusor muscle would do without the sphincters present, we are going to do a thought experiment. We are going to take a person who has a bladder that is half filled. Insert an indwelling catheter through the urethra into the bladder. This is a rigid tube, so the internal and external sphincters cannot constrict or dilate. The presence of the catheter negates the sphincters. Because of gravity and what we are about to explain about the detrusor, urine drains into the catheter and into the toilet. At this point the bladder is empty and the sphincters are "open" because of the catheter.

We then attach to the end of the catheter a three-way stopper. On one end of the three-way stopper, we attach a syringe filled with 500 ccs of water (it's a big syringe). On another end of the three-way stopper, we attach a pressure monitor. On the third end of the three-way stopper is a release valve through which urine may be emptied. We also magically attach electrodes on the detrusor muscle to measure electrical activity.

What this allows us to do is increase the volume in the bladder and measure the **intravesicular pressure**. What is the relationship between adding volume and the pressure in the bladder? That's what we're answering. And we wouldn't be spending so much time on it if the answer were "proportional to the volume." The experiment goes like this—add 50 ccs of fluid, measure the pressure; add 50 ccs of fluid, measure the pressure—for the entire 500 ccs.

When we move from zero to 50 ccs there is a moderate increase in intravesicular pressure. When a person voids, even though they feel like they are done emptying the bladder, the bladder doesn't fully empty. This zero to 50 ccs business is an artifact of draining the bladder in the first place. From about 50 ccs to 300 ccs there is almost no change in pressure. This high compliance reflects **relaxation of the detrusor**. Those electrodes would read little activity. A normal post-void residual (what is left in the bladder after a "complete" void) is usually between 50 ccs and 100 ccs. A person feels the urge to urinate after 300 ccs, and it increases significantly the more urine that is added. At volumes greater than 400 ccs, additional increases in volume produce steep increases in passive pressure.

Below 300 ccs, additional volume causes only miniscule increases in pressure. More pressure change would be expected if stretch were the signal that induced detrusor contraction. Above 300 ccs, the additional volume causes large increases in intravesicular pressure disproportionate to that caused by passive stretch of smooth muscle alone. Bladder tone, how hard the detrusor contracts, is in part a

response to being stretched. This stretched-induced contraction is independent of bladder innervation. However, it is very obvious that more than stretch-induced contraction regulates bladder tone.

If there were no autonomic inputs, the bladder would contract proportionately to the degree it is stretched. But there are autonomic inputs. And the bladder stretch IS the signal that regulates the autonomics. The detrusor sends out signals to the spinal cord and the pons, which in turn feed back on the **bladder and urethral sphincters**, as discussed in the next section.

Micturition Physiology

Micturition is immensely under somatic control despite the mostly autonomic innervation of the bladder and urethral sphincters. All of urinary physiology comes down to either filling up the bladder—the storage phase—or emptying the bladder—the voiding phase. The person is in voluntary control of when the bladder moves from the storage phase to the voiding phase. The bladder can give extremely strong signals to the cortex, informing the person that they really should void, but it is the higher cortical regions that decide when the switch is made. This is unlike most visceral organs where there is little cortical input. Most visceral organs, such as the entirety of the gut and gut-tube structures, function on autonomic inputs and spinal cord reflexes only. Gut regulation is done without the awareness of the person. The bladder is very different.

During the **storage phase** urine is being added to the bladder from the ureters. Both urethral sphincters are closed, so no urine leaves. During neuronal development, from infancy until about five years of age, the spinal cord develops spinal reflexes called **guarding reflexes**. These reflexes are learned, mature in childhood, and are what allow for continence. Potty training is not just teaching a child to "hold it in" (which would be somatic contraction of the extrinsic sphincter). Potty training is also developing these guarding reflexes which promote unconscious (autonomic) continence. As the bladder fills with urine, the detrusor is stretched. That stretch generates an afferent signal to the spinal cord. Stretch of the detrusor generates only a small signal, and that small signal can reach only the spinal cord. Bladder afferents to the spinal cord **stimulate sympathetic fibers** and **stimulate pudendal fibers**. No mention of parasympathetics. The guarding reflex is an automatic reflex, learned in childhood, that promotes contraction of both internal and external sphincters. The stretch of the detrusor, which inherently increases detrusor tone (as discussed above), develops a reflex arc that decreases detrusor contraction tone. The stretch of the bladder increases the efferent signaling from the detrusor (it sends out more messages at more stretch) and that signaling results in decreased stimulus to contract. As it is stretched, it yells louder, but does not contract stronger.

As the bladder continues to fill, stretch receptors reinforce the guarding reflex. At a critical level of bladder distention, however, the system flips into the **voiding reflex**. The set point for that critical level of bladder distention is set by the **pontine micturition center** (PMC). Manipulation of the PMC in experimental models can change the volume of urine at which the voiding reflex turns on without impacting the magnitude of the response. The detrusor sends small signals to the spinal cord (guarding reflex) but also sends signals to the PMC. All of the signals the detrusor sends to the spinal cord are to keep urine in. The PMC monitors the detrusor signal until a threshold is met. When that threshold is met, the PMC takes over. The PMC projections **inhibit sympathetics** (relaxing the internal sphincter), **inhibit somatic** (relaxing the external sphincter), and **stimulating parasympathetics** (contracting the detrusor). This voiding reflex would result in elimination of the bladder. When the voiding reflex fires, it both cancels the guarding reflex and stimulates the bladder to contract. Now, stretch-induced contraction and parasympathetic-induced contraction summate to extreme forces AND the urethral sphincters open.

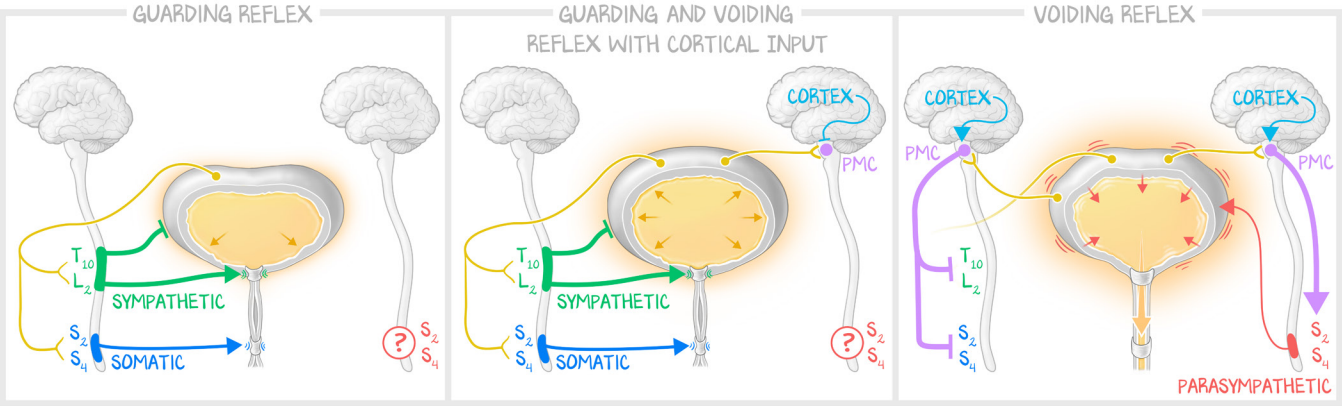

Figure 2.2: Micturition Reflexes
As urine volumes increase in the detrusor, the signal to the guarding reflex increases, ensuring that sympathetic and somatic stimulation silences the bladder contraction. Above a critical volume, the guarding reflexes are still reinforced by detrusor contractions, but the signal is intense enough to activate voiding reflex autonomic arc from the pontine micturition center. Cortex inhibits that center. When cortex disinhibits the pontine micturition center, it silences the guarding reflex, stimulates the voiding reflex, and facilitates somatic relaxation of the external sphincter.

But you said it was under somatic control . . .

Indeed. That explains the reflex arc. In live humans (i.e., not experimental models), the generation of the critical signal to the PMC does come from distention of the bladder. But that distention of the bladder does not trigger the PMC-triggered voiding reflex, because **inhibition from cortical regions prevents it**. The details of that complex neural network are not for you to learn. But here's how it works from a practical standpoint.

During the storage phase, the guarding reflex keeps you continent. As more urine fills the bladder, the pudendal nerve makes you aware. You can go about your business, not paying attention to your bladder, and remain continent because of the guarding reflex. As the bladder gets fuller and fuller, the bladder reinforces the guarding reflex, so you stay continent. At the same time, the pudendal nerve is giving you more and more signals that you should pee. When the bladder volume gets over 300 ccs, you feel the urge to void. Above 500 ccs and the urge is strong. Close to 1,000 ccs, that sensation isn't an urge, it is frank pain.

You get to a place where it is socially acceptable to void. You take off your bottoms, and sit on the toilet (so both guys and girls can visualize). Now, pee. What you sense is the decision to void, the relaxation of your pelvic muscles, a little bit of time goes by, and . . . urine. It was a lot of work to get that stream started. And if you now don't concentrate on the stream, the stream keeps streaming. It isn't a lot of work to keep the stream going.

What happened? The guarding reflex kept you continent. The bladder, the whole time was screaming at the PMC to initiate the voiding reflex. Your brain said no to the PMC. When you sat down to pee, you decided it was time. You voluntarily relaxed the external sphincter. When you did that, your brain also stopped telling the PMC no. The voiding arc was strong, and now without your cortex saying no, the PMC unleashed the full force of the voiding reflex.

The **voiding phase** is initiated by cortical control over the external sphincter to relax, and by cortical control over the PMC to stop. The voiding phase continues because the PMC takes over the autonomics and maintains control continuing the void without cortical input.

In addition (we left this out because it complicates things unnecessarily, but is interesting to say), stimulation of the PMC voiding reflex occurs because the relaxation of the external sphincter brings urine into contact with the posterior urethra. As urine is passing through the urethra, that signal is maximized and propagates the PMC voiding reflex (which is why it is hard to start, but easy to continue voiding).

Finally, if you choose to stop voiding mid-void, you can. You contract the external sphincter, stopping the flow of urine. Your brain tells the PMC no again. At this point the guarding reflex is less than it was (because you voided some urine) but you can consciously stop voiding and still maintain continence.

Other Forces of Micturition

In addition to the intended mechanisms, there is also the ability to **translate abdominal pressure** onto the bladder by performing a Valsalva maneuver. This increase in intra-abdominal pressure can give the bladder an extra push to overcome the relaxed state of the detrusor (not contracting when it should) or the contracted state of the internal sphincter (not relaxing when it should).

For women who get pregnant, abdominal forces can matter a lot more than just that. Abdominal pressure is translated to the detrusor (which forces urine out), but also to the sphincters (which keeps urine in). This is why humans don't normally pee when they sneeze. The **pelvic floor** is a series of skeletal muscles (do not learn their names) that the urethra, vagina, and anus pass through. Men have a pelvic floor also, but men lack the ability to alter the pelvic floor the way women can—pregnancy. If the pelvic floor gets stretched out by pregnancies or deliveries, gently referred to as "**pelvic floor relaxation**," the support for the bladder, uterus, and rectum becomes compromised. We're going to focus on the bladder here. The pelvic floor is skeletal muscles. The external urethral sphincter is skeletal muscle. They are both in the same vicinity as one another. The external urethral sphincter is not part of the pelvic floor.

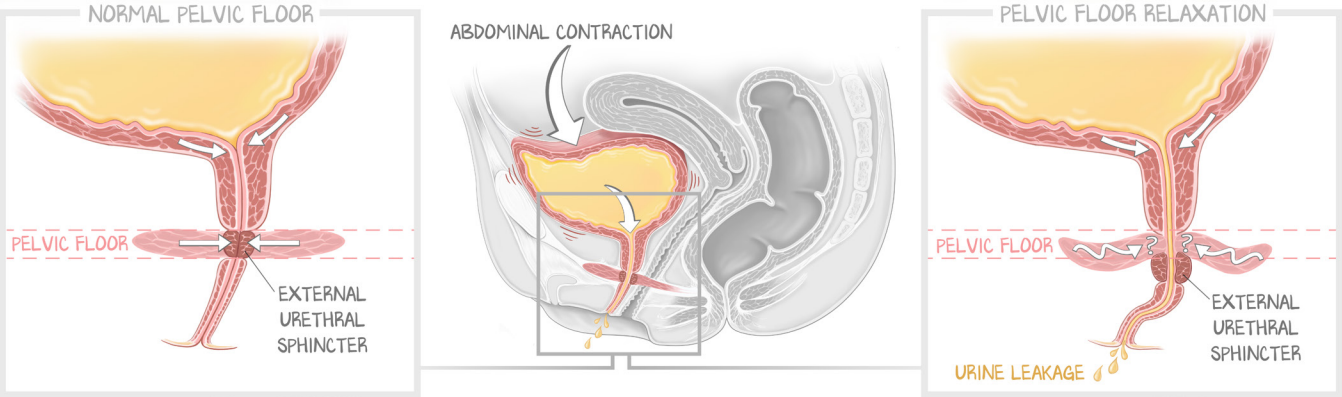

Figure 2.3: Pelvic Floor Relaxation
Abdominal contraction would force urine out of the bladder if there were no sphincters. In a normal pelvic floor, that abdominal pressure is also translated to both the internal and external sphincters, preventing the spilling of urine. In pelvic floor relaxation, where the external sphincter no longer feels the abdominal contraction, the internal sphincter is insufficient to block the exit of urine, and some urine leaks out.

If the bladder falls through the pelvic floor, called a **cystocele**, the most inferior portion falls through first. This would be the urethra. If enough of the urethra ends up under the pelvic floor, then when the abdominal muscles are contracted, the forces of that contraction will be translated to the bladder only, and not the sphincters. This causes stress incontinence (which is discussed next in the pathology section).

Men who have prostate surgery can also develop pelvic floor relaxation. But because there is a much higher incidence of pregnancy in women than there is prostate surgery in men, and because the age at which pregnancy occurs is much lower than prostate surgery in men, pelvic floor relaxation issues are mainly of female concern.

Problems with Micturition

Stress incontinence affects women who have had babies, and represents a consequence of pelvic floor relaxation. The ligaments between the uterus and the bladder as well as the pelvic floor muscles have been stretched by pregnancy and delivery. Now, the internal sphincter falls into the pelvis from a weakened muscular floor. When the woman increases intra-abdominal pressure (sneezing, playing tennis, coughing), the intra-abdominal pressure is applied to the detrusor like normal. But with the internal sphincter no longer above the pelvic floor, the force of the abdominal pressure is translated ONLY to the detrusor, and not to the sphincter. Briefly, there is enough force to eke out a little urine. This is treatable by strengthening the pelvic floor (exercise, pessaries) or by surgery. Stimulating or inhibiting sympathetics would not do anything—the guarding reflex is intact. Stimulating or inhibiting parasympathetic would not do anything—the voiding reflex is intact. Diagnosis is made with a Q-tip test, which demonstrates urethral hypermobility.

Overflow incontinence (also called hypotonic bladder or neurogenic bladder) is caused by the detrusor being unable to contract. The guarding reflex is the local reflex arc that reinforces detrusor relaxation and internal sphincter contraction. While the detrusor is innervated by the parasympathetic fibers, without input from the PMC there is nothing to signal parasympathetic activity. If the spinal cord is damaged, none of the spinal cord tracts can work. That means the detrusor cannot send a signal to the PMC. The PMC cannot send a signal to the parasympathetics. And the pudendal sensory fibers cannot reach cortex. That means the bladder fills and fills, stretching the detrusor. Remember detrusor physiology from above? Independent of innervation, the detrusor will contract from being stretched.

When the tensile pressure finally reaches a maximum, the detrusor, rather than exploding, forces a little urine out. The contraction of the detrusor overcomes the force of the sphincters, and a small amount of urine is lost. That small decrease in volume reduces the stretch of the detrusor so the force it generates is just under the force of the sphincters—until more urine is made, when the process happens again. The equilibrium point is a **huge, distended, thin-walled bladder.** These patients will have **large post-void residuals**. In this case, the detrusor isn't contracting enough because it cannot get the parasympathetic signal via the PMC. These patients have an intact detrusor and intact muscarinic receptors. **Muscarinic agonists** such as **bethanechol** focus on the muscarinic receptors and cause detrusor contraction. **Beth-Ann, Call** your bladder and tell it to hurry up! (Discussed in General Pharmacology #9: *Cholinergics (PNS)*.)

We've set neurogenic bladder up as a very discrete disease—big bladder, no sensation, spinal cord problem. We want you learning neurogenic bladder and overflow incontinence as the same thing. But there are ways of getting a similar picture but with the spinal cord intact. For patients who develop overflow incontinence and **can feel the distension**, look for these mechanisms. First, **α_1 stimulation** will prevent the internal sphincter from opening. So while the PMC may be telling the spinal cord to do the right thing, **drugs** that stimulate α_1 receptors (cocaine, amphetamine, MDMA) can cause the inability to urinate, allowing the bladder to get distended. Second, **antagonizing muscarinic receptors** (giving too much urge incontinence medication, for example) will result in the parasympathetic discharge, but the bladder won't listen. This is the major risk of giving medications such as oxybutynin (below). Third, **obstruction of the urethra** (as occurs with BPH, discussed in the next lesson) will cause the bladder to fill. The backpressure on the urethra is so great that even though the detrusor system is intact, and it is trying to void, the detrusor must overcome the pressure of the obstruction. This is why some patients with BPH may **strain** to get a void. The straining increases intra-abdominal pressure and helps the detrusor overcome the obstruction. In this instance it is the obstruction, not faulty contractions, that is the problem. Muscarinic agonists like bethanechol would not help.

Urge incontinence (also called hypertonic bladder or overactive bladder) is caused by **involuntary** and **inappropriate** detrusor muscle contractions. This happens in otherwise healthy people and the knowledge of the pathogenesis is limited. What we do know is that the bladder spasms at inappropriate volumes and without cortical signaling that it is okay to do so. It is almost as if the voiding reflex activates without cortical control. This causes strong urges to urinate, often with leakage of urine. The detrusor is contracting too much. The detrusor contracts in response to ACh release from the parasympathetics. To quiet it, we would need to **inhibit M_3 receptors** using **muscarinic antagonists.** These medications are **oxybutynin,** tolterodine, and solifenacin. Too much of these medications could induce an obstructive uropathy via neurogenic bladder.

Irritation incontinence is a form of urge incontinence. It is caused by inflammation of the bladder, called cystitis. You know that by a different name—urinary tract infection. The urgency and frequency associated with urinary tract infections are products of inappropriate and involuntary detrusor muscle contractions. We want you learning this as something different than urge incontinence. If there is an infection you need to treat the infection and flush the bladder, not give muscarinic antagonists to keep the urine stagnant, worsening the infection. Urgency, frequency, dysuria, and a urinalysis showing WBC and organisms is cystitis, not urge incontinence.